

# Finding Fanconi: the hunt for the cause of autosomal dominant renal Fanconi syndrome

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The human genome lays down the blueprint for our physiology and thus provides a framework by which to study genetic-based diseases. Researchers have focused recently on a region that may be responsible for a debilitating kidney disease — autosomal dominant renal Fanconi syndrome (RFS). In RFS, the proximal tubules of the kidney are functionally impaired. This causes many essential compounds that would normally be returned to the bloodstream to instead be excreted into the urine and removed from the body.

Genetic as well as environmental factors can lead to the development of RFS. An autosomal dominant form of RFS has been observed in several families; one of these was used as the basis for an attempt to find a genetic locus to the disease. The inheritable form of the syndrome is of particular interest for researchers because it can potentially provide insight into the workings of the proximal tubules. Correlating a disease with a genetic mutation is not an easy task. To successfully map a disease gene on the human genome, it is necessary to have a series of genomic landmarks. This has been one of the major accomplishments of the Human Genome Project; over 10,000 polymorphic markers have been identified and contextually placed onto framework maps.

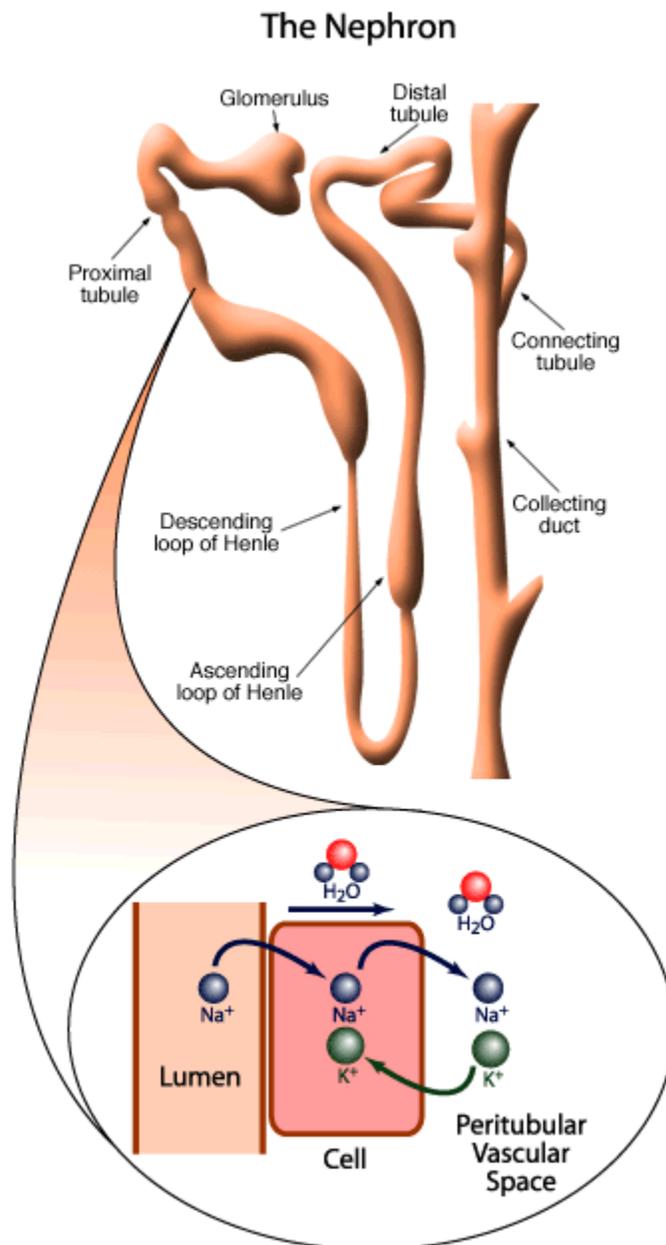
To find the region associated with RFS, DNA samples from the afflicted family were initially scanned using polymorphic markers that were distributed throughout the genome. Linkage analysis implicated marker D15S659, which is found on the long arm of chromosome 15. This initial hit gave researchers a rough area to further scrutinize by conducting a

more detailed screen with 24 localized markers.

From the secondary screen, two markers—D15S182 and D15S537 [[http://www.ncbi.nlm.nih.gov/Coffeebreak/CB22\\_Fanconi/staticbld26.html](http://www.ncbi.nlm.nih.gov/Coffeebreak/CB22_Fanconi/staticbld26.html)] — were determined to exhibit the greatest correlation with RFS.

Genes in the 15q15.3 region are now being considered as candidates for association with RFS. By definitively associating autosomal dominant RFS with a gene, new insights into the pathology of the disease can be gained. One possible candidate gene, HSPC129, [<http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?!=51496>] codes for a hypothetical protein [<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=7705461&db=Protein&dopt=GenPept>] with unknown function.

Further clues as to the possible function of an uncharacterized protein can be discerned by comparing it with other, characterized proteins (e.g., using NCBI's Related Sequences feature). In the case of HSPC129, one of the proteins it shares similarity with is the yeast protein Psr2P. This protein is involved in the indirect regulation of transmembrane sodium transportation. Active transport of ions such as sodium takes place in the proximal tubules of the kidneys and is a key component of healthy kidney function. Could HSPC129 also be involved in the regulation of ion transport in the kidneys similar to Psr2P regulation of sodium transportation in yeast cells? Although the presence of HSPC129 in the proximal tubules of the kidneys remains to be determined, studies on Psr2P in yeast may give insight into human HSPC129 function and possibly lead to a treatment for autosomal dominant RFS.



**Active sodium transportation in the proximal tubule** The kidneys are responsible for a number of important regulatory functions such as the maintenance of ion levels in the body, water retention/removal, waste excretion, blood pressure regulation, and maintenance of proper blood acidity. Nephrons are the functional unit of the kidney. Within the proximal tubule portion of the nephron is found the highest concentration of sodium transporters. These transporters are responsible for the active reabsorption of sodium ions from filtrate present in the lumen of the nephron. Water is absorbed passively during this process due to the accumulation of sodium in the peritubular spaces. Any disruption to this system would result in the loss of large amounts of water, sodium, and other ions.

## Important Links

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### Live PubMed searches

- (1) Mapping RFS
- (2) Kidney disease clinical trials
- (3) REVIEWS

### Roadmap

- (1) Original Paper
- (2) The first marker's location in the genome
- (3) Secondary screen implicates two markers [[http://www.ncbi.nlm.nih.gov/Coffeekbreak/CB22\\_Fanconi/staticbld26.html](http://www.ncbi.nlm.nih.gov/Coffeekbreak/CB22_Fanconi/staticbld26.html)]
- (4) HSPC129 gene in Locus Link [<http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=51496>]
- (5) Sequence of the hypothetical protein [<http://www.ncbi.nlm.nih.gov/entrez/viewer.cgi?val=7705461&db=Protein&dopt=GenPept>]
- (6) Related sequences
- (7) Psr2P, a yeast gene
- (8) Function of Psr2P

### Additional NCBI resources

- UniSTS
- Medline Plus [<http://www.nlm.nih.gov/medlineplus/ency/article/000333.htm>]
- NIDDK [<http://www.niddk.nih.gov/index.htm>]